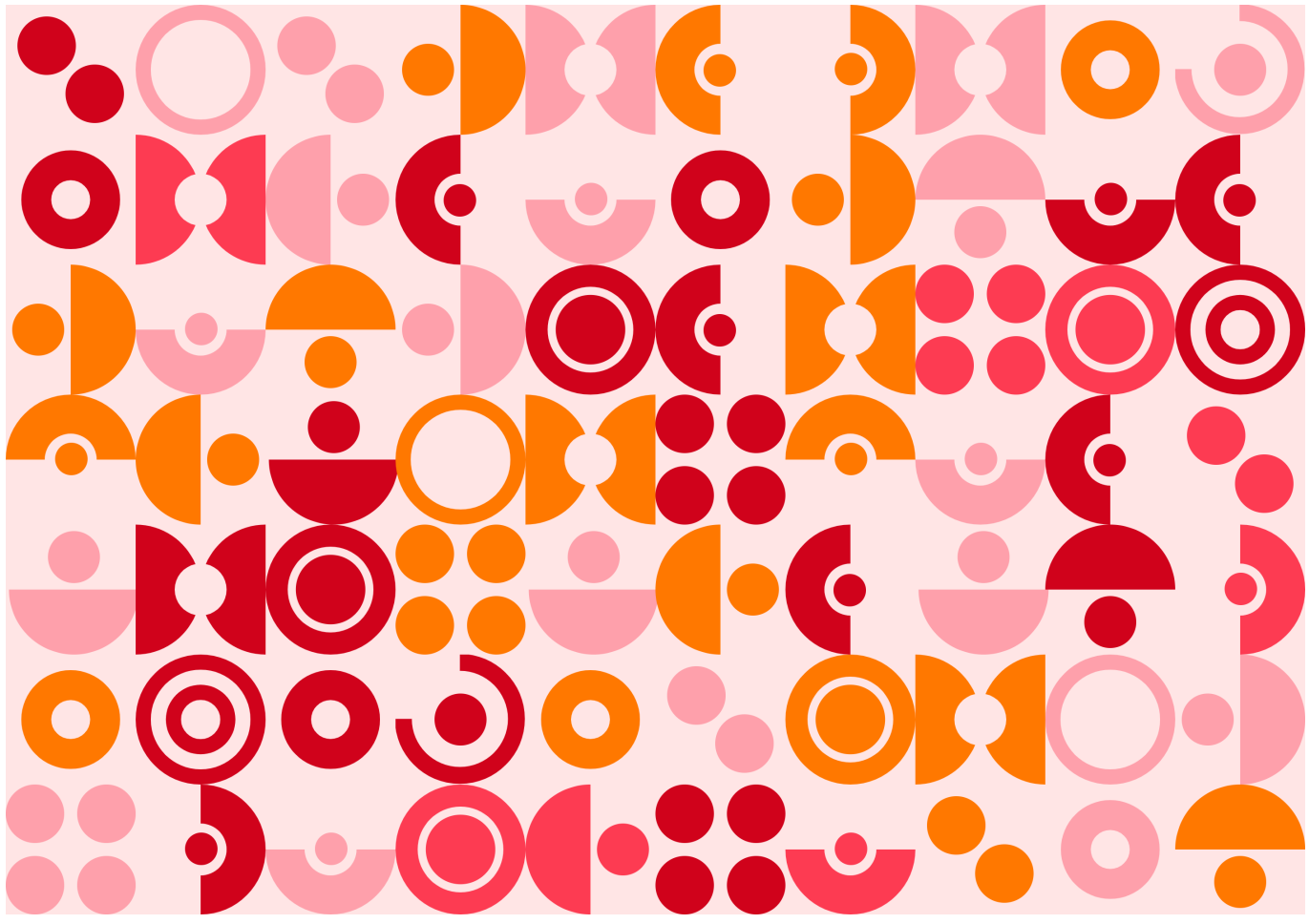

Pyrls Press — 2023

Cholesterol Management for ASCVD Risk Reduction

Algorithms

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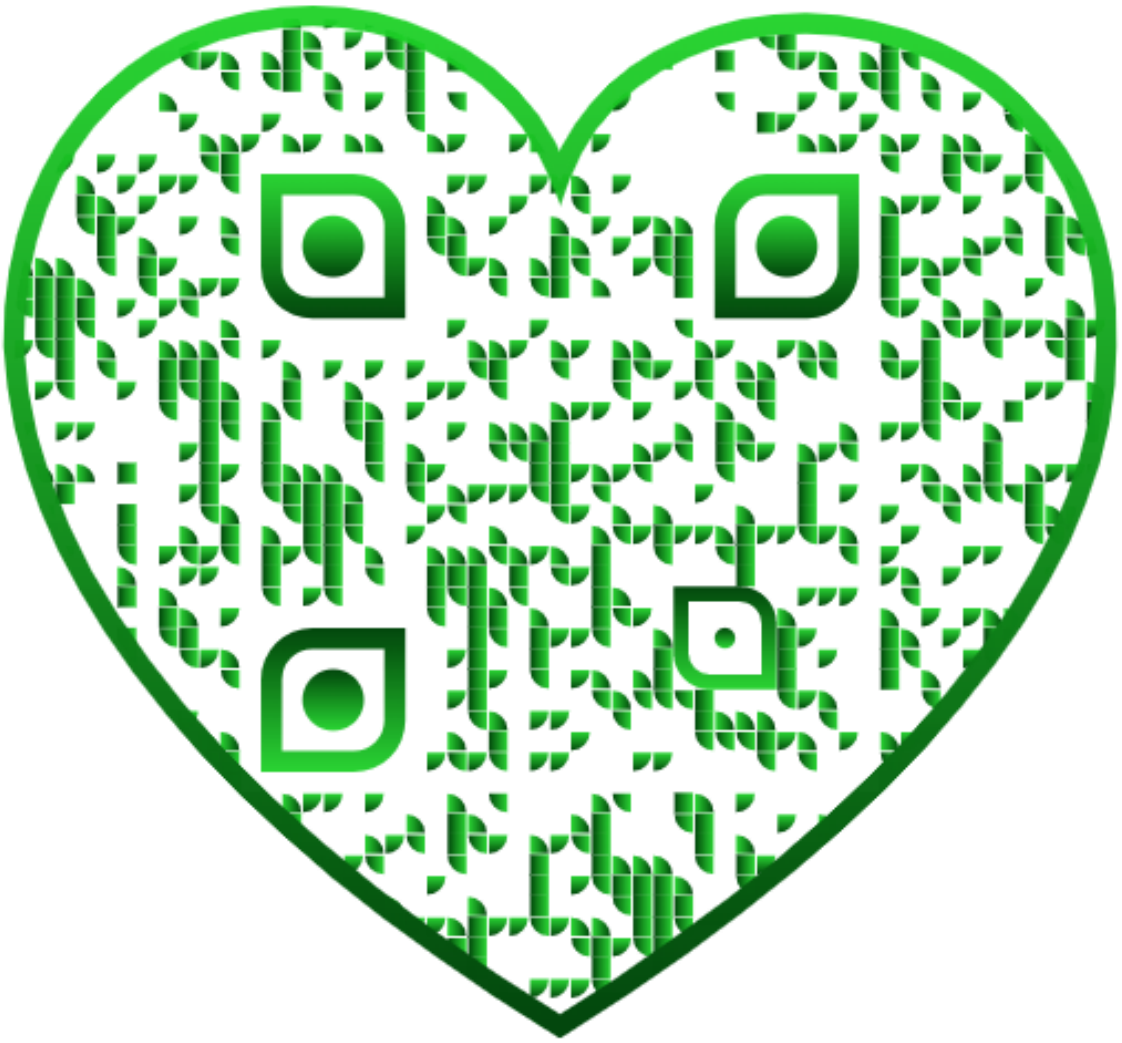

Scope of Document and Disclaimer

This document contains a collection of cholesterol management for ASCVD risk reduction algorithms recreated from algorithms and recommendations from the 2018 AHA/ACC/multisociety Guideline on the Management of Blood Cholesterol and the 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-C Lowering in the Management of ASCVD Risk.

Readers should note that this document was published in **February 2023**, and some of the information in this document is **subject to change.**

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We thank you so much!
The Pyrls Team

Questions, comments, feedback?
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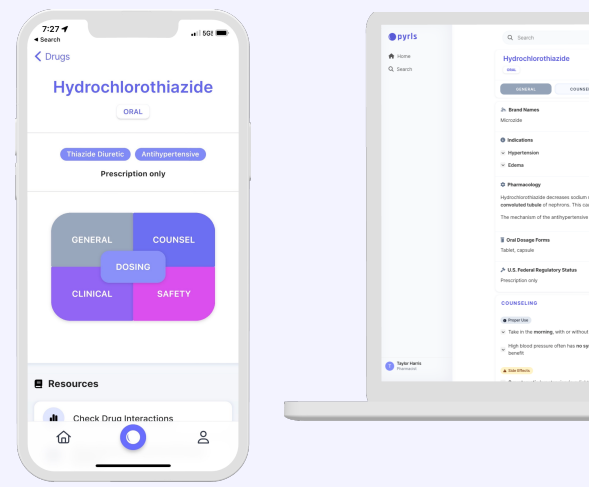

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Patient Subgroups

Individual algorithms on the ensuing pages are provided for the patient subgroups listed below.

Secondary ASCVD Prevention

- **ASCVD Not at Very High Risk**
- **Very High Risk ASCVD**
- **Baseline LDL-C ≥ 190 mg/dL without clinical/genetic FH diagnosis**
- **Baseline LDL-C ≥ 190 mg/dL with clinical/genetic FH diagnosis**

Primary ASCVD Prevention

- **Baseline LDL-C ≥ 190 mg/dL**
- **Adults with Diabetes and Baseline LDL-C < 190 mg/dL**
- **Adults without Diabetes and Baseline LDL-C 70-189 mg/dL**

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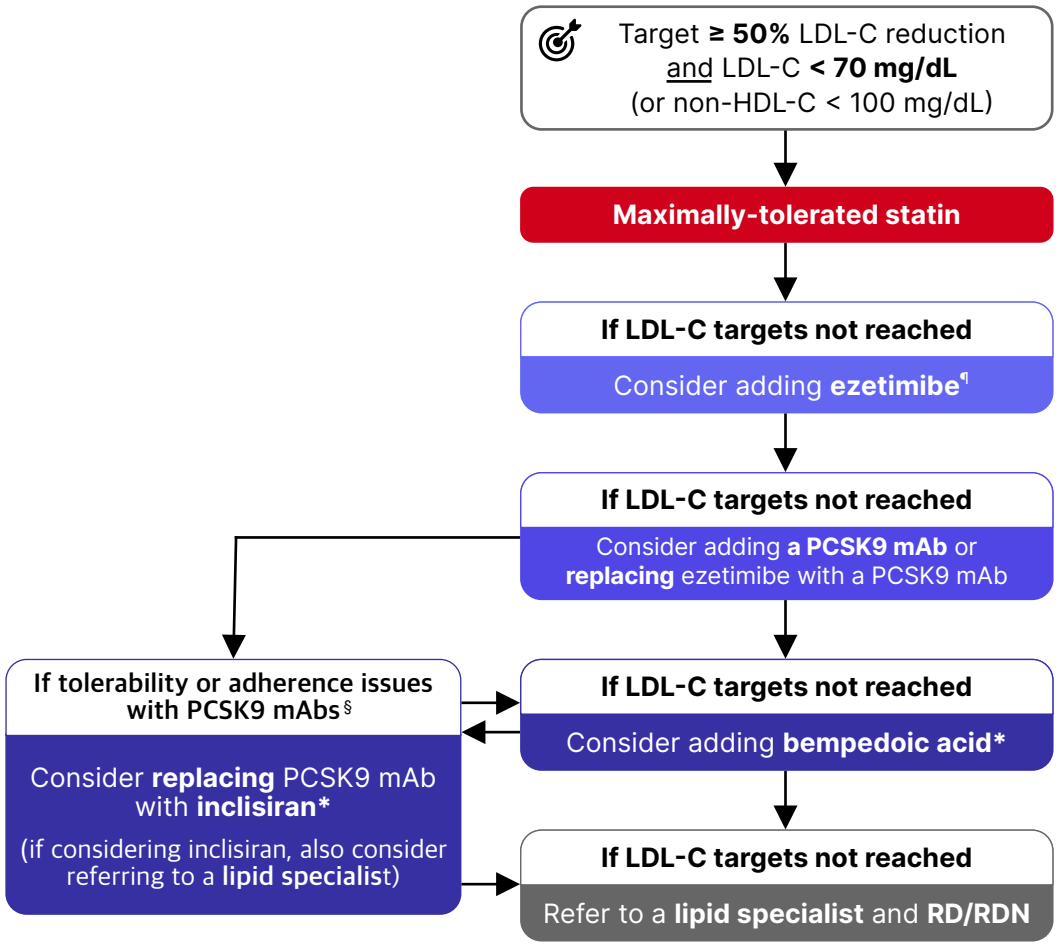
Secondary ASCVD Prevention: ASCVD Not at Very High Risk †


Target ≥ 50% LDL-C reduction
and LDL-C < 70 mg/dL
(or non-HDL-C < 100 mg/dL)
Maximally-tolerated statin
If LDL-C targets not reached
Consider adding ezetimibe¶
If LDL-C targets not reached
Consider adding a PCSK9 mAb or replacing ezetimibe with a PCSK9 mAb
If tolerability or adherence issues with PCSK9 mAbs§
Consider replacing PCSK9 mAb with inclisiran*
(if considering inclisiran, also consider referring to a lipid specialist)
If LDL-C targets not reached
Consider adding bempedoic acid*
If LDL-C targets not reached
Refer to a lipid specialist and RD/RDN

† Very high-risk is defined as either a history of multiple major ASCVD events or one major ASCVD event with multiple high-risk conditions

High-Risk Conditions
- Age ≥ 65 years
- Heterozygous familial hypercholesterolemia
- History of prior CABG surgery or PCI outside of the major ASCVD event(s)
- Diabetes
- Hypertension
- Chronic kidney disease
- History of congestive heart failure
- Current smoker
- Persistently elevated LDL-C (≥ 100 mg/dL) despite max-tolerated statin and ezetimibe

Major ASCVD Events
- Any recent ACS (in last 12 months)
- History of MI *(other than recent ACS)*
- History of ischemic stroke
- Symptomatic PAD

¶ Simultaneous addition of two agents may be warranted in certain patients requiring greater LDL-C reduction than is likely achievable with one added therapy alone.

*** No cardiovascular outcomes data** currently available for these agents *(for inclisiran, trial results are expected in 2026 and 2027)*

§ It should be noted that **inclisiran** is an alternative option for patients who are unable to fully benefit from PCSK9 mAbs due tolerability or adherence issues. Tolerability and adherence issues include **inability to self-administer.** PCSK9 mAbs are currently the **preferred** over inclisiran based on available safety, efficacy, and cardiovascular outcomes data. If inclisiran is prescribed, it should **replace** the PCSK9 mAb, **not be used together**.

ACS: acute coronary syndrome
ASCVD: atherosclerotic cardiovascular disease
CABG: coronary artery bypass graft
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
MI: myocardial infarction
PAD: peripheral artery disease
PCI: percutaneous coronary intervention
PCSK9 mAb: proprotein convertase subtilisin/kexin type 9 monoclonal antibody
RD: registered dietitian
RDN: registered dietitian nutritionist

Reference: [1] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
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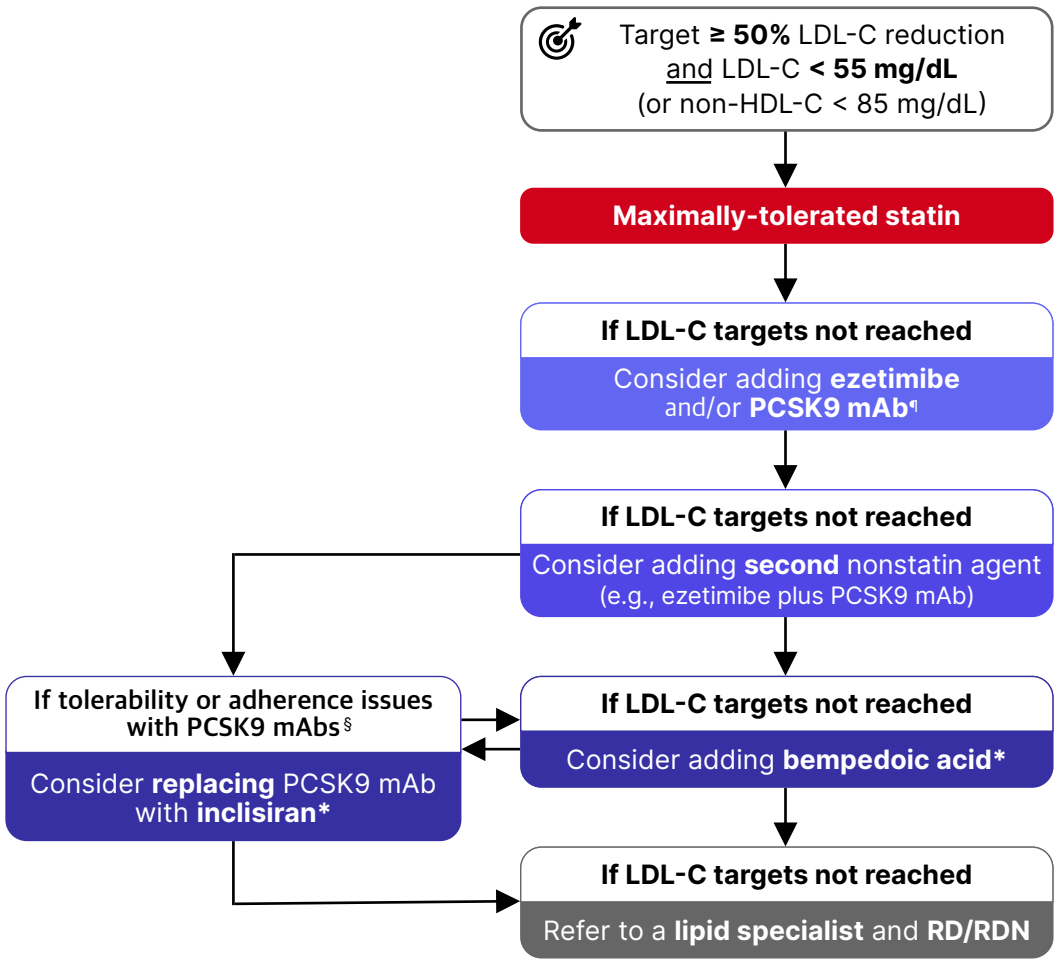
Secondary ASCVD Prevention: Very High Risk ASCVD †


Target ≥ 50% LDL-C reduction
and LDL-C < 55 mg/dL
(or non-HDL-C < 85 mg/dL)
Maximally-tolerated statin
If LDL-C targets not reached
Consider adding ezetimibe and/or PCSK9 mAb¶
If LDL-C targets not reached
Consider adding second nonstatin agent (e.g., ezetimibe plus PCSK9 mAb)
If tolerability or adherence issues with PCSK9 mAbs§
Consider replacing PCSK9 mAb with inclisiran*
If LDL-C targets not reached
Consider adding bempedoic acid*
If LDL-C targets not reached
Refer to a lipid specialist and RD/RDN

† Very high-risk is defined as either a history of multiple major ASCVD events or one major ASCVD event with multiple high-risk conditions

High-Risk Conditions
- Age ≥ 65 years
- Heterozygous familial hypercholesterolemia
- History of prior CABG surgery or PCI outside of the major ASCVD event(s)
- Diabetes
- Hypertension
- Chronic kidney disease
- History of congestive heart failure
- Current smoker
- Persistently elevated LDL-C (≥ 100 mg/dL) despite max-tolerated statin and ezetimibe

Major ASCVD Events
- Any recent ACS (in last 12 months)
- History of MI *(other than recent ACS)*
- History of ischemic stroke
- Symptomatic PAD

¶ Simultaneous addition of two agents may be warranted in certain patients requiring greater LDL-C reduction than is likely achievable with one added therapy alone. If considering either ezetimibe or PCSK9 mAb, consider the following:
- **Ezetimibe** may be preferred as the initial nonstatin agent in those who require **< 25%** additional LDL-C reduction or those with recent ACS (< 3 months)
- A **PCSK9 mAb** may be preferred as the initial nonstatin agent in those who require **> 25%** additional LDL-C reduction

*** No cardiovascular outcomes data** currently available for these agents *(for inclisiran, trial results are expected in 2026 and 2027)*

§ It should be noted that **inclisiran** is an alternative option for patients who are unable to fully benefit from PCSK9 mAbs due tolerability or adherence issues. Tolerability and adherence issues include **inability to self-administer.** PCSK9 mAbs are currently the **preferred** over inclisiran based on available safety, efficacy, and cardiovascular outcomes data. If inclisiran is prescribed, it should **replace** the PCSK9 mAb, **not be used together**.

ACS: acute coronary syndrome
ASCVD: atherosclerotic cardiovascular disease
CABG: coronary artery bypass graft
HDL-C: high-density lipoprotein cholesterol
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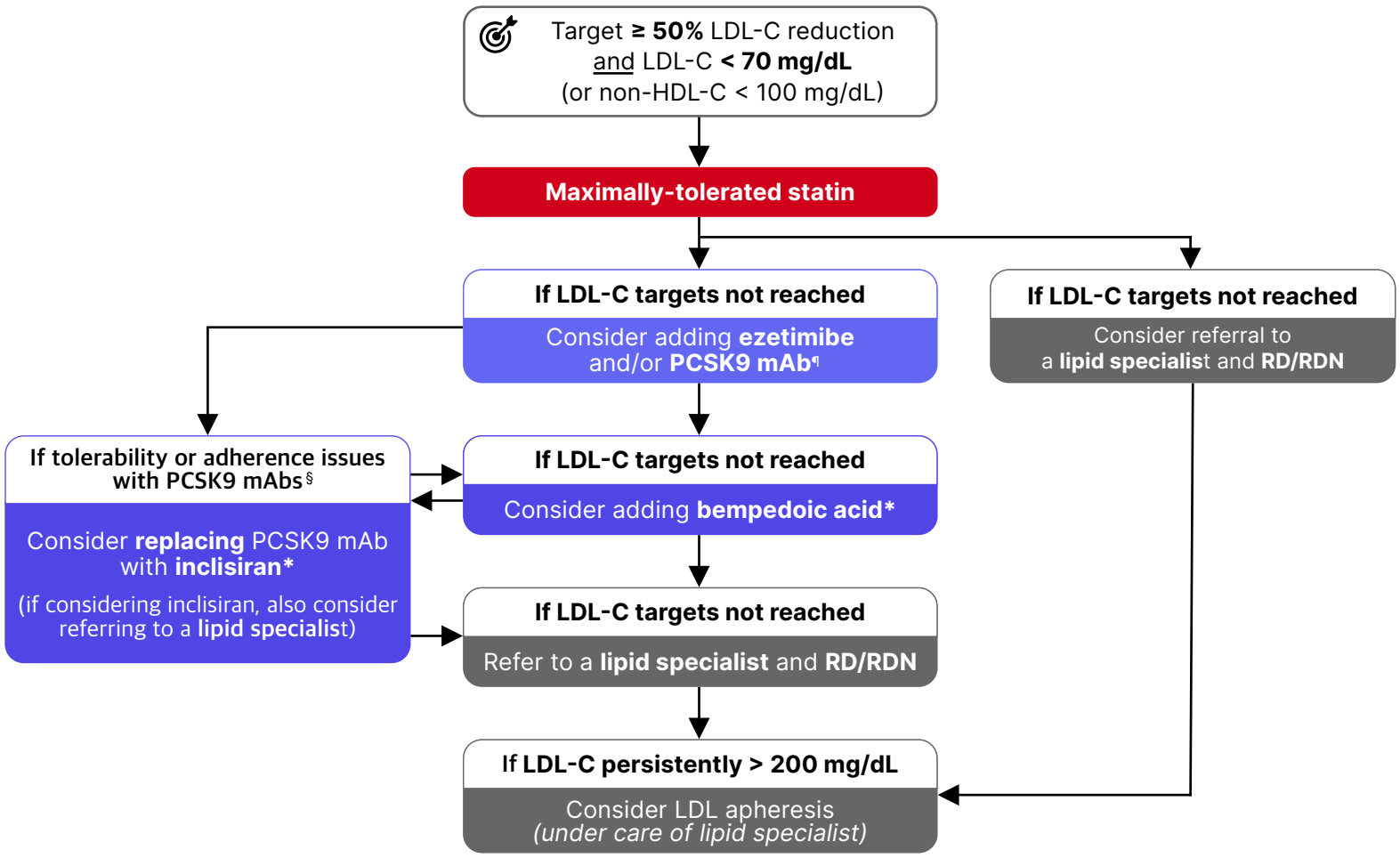
Secondary ASCVD Prevention: Baseline LDL-C ≥ 190 mg/dL without clinical/genetic FH diagnosis


Target ≥ 50% LDL-C reduction
and LDL-C < 70 mg/dL
(or non-HDL-C < 100 mg/dL)
Maximally-tolerated statin
If LDL-C targets not reached
Consider adding ezetimibe and/or PCSK9 mAb¶
If LDL-C targets not reached
Consider referral to a lipid specialist and RD/RDN
If tolerability or adherence issues with PCSK9 mAbs§
Consider replacing PCSK9 mAb with inclisiran*
(if considering inclisiran, also consider referring to a lipid specialist)
If LDL-C targets not reached
Consider adding bempedoic acid*
If LDL-C targets not reached
Refer to a lipid specialist and RD/RDN
If LDL-C persistently > 200 mg/dL
Consider LDL apheresis
(under care of lipid specialist)

¶ Simultaneous addition of two agents may be warranted in certain patients requiring greater LDL-C reduction than is likely achievable with one added therapy alone. If considering either ezetimibe or PCSK9 mAb, consider the following:

- **Ezetimibe** may be preferred as the initial nonstatin agent in those who require **< 25%** additional LDL-C reduction
- A **PCSK9 mAb** may be preferred as the initial nonstatin agent in those who require **> 25%** additional LDL-C reduction

*** No cardiovascular outcomes data** currently available for these agents *(for inclisiran, trial results are expected in 2026 and 2027)*

§ It should be noted that **inclisiran** is an alternative option for patients who are unable to fully benefit from PCSK9 mAbs due tolerability or adherence issues. Tolerability and adherence issues include **inability to self-administer.** PCSK9 mAbs are currently the **preferred** over inclisiran based on available safety, efficacy, and cardiovascular outcomes data. If inclisiran is prescribed, it should **replace** the PCSK9 mAb, **not be used together**.

ASCVD: atherosclerotic cardiovascular disease
FH: familial hypercholesterolemia
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
PCSK9 mAb: proprotein convertase subtilisin/kexin type 9 monoclonal antibody
RD: registered dietitian
RDN: registered dietitian nutritionist

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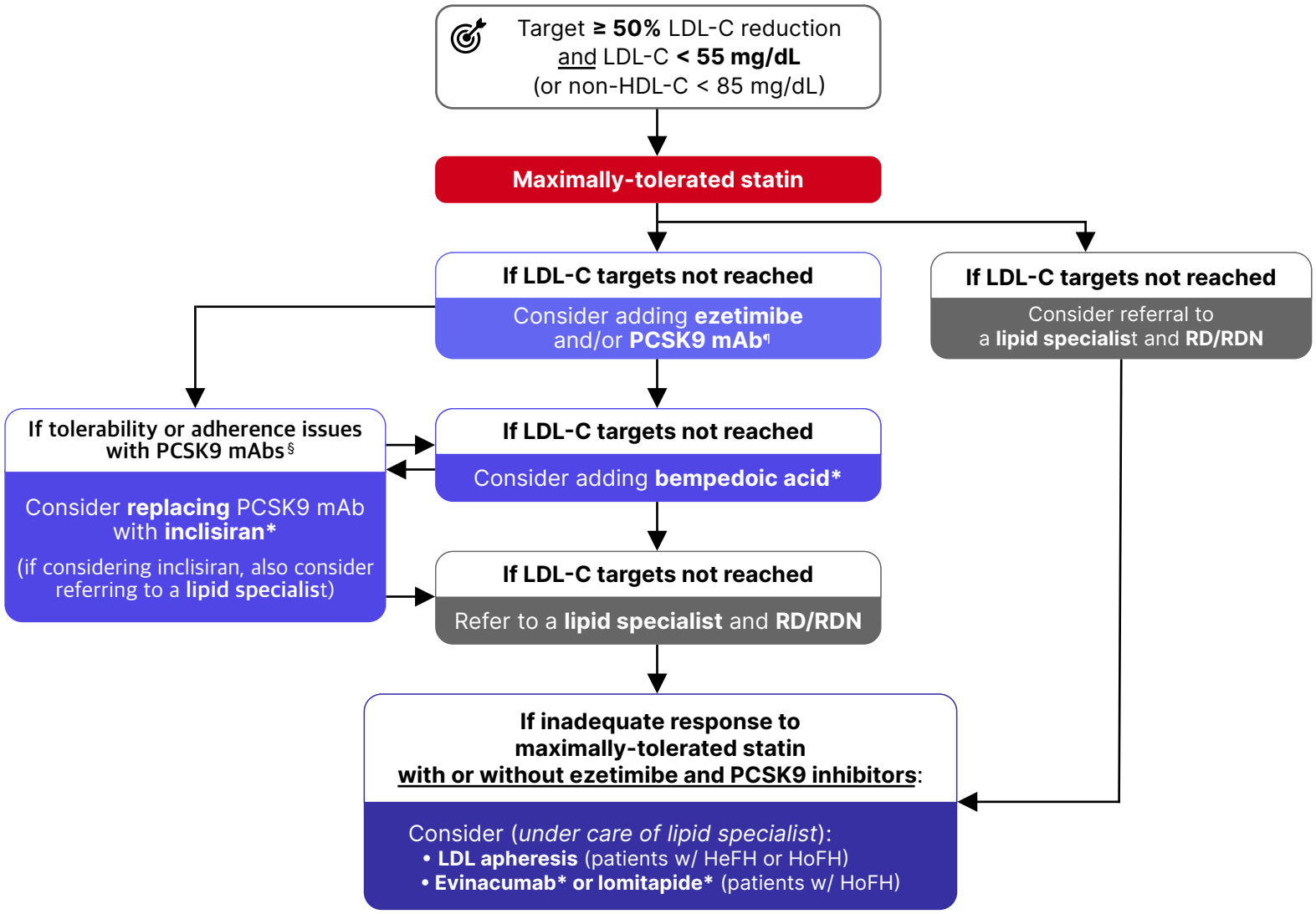
Secondary ASCVD Prevention: Baseline LDL-C ≥ 190 mg/dL with clinical/genetic FH diagnosis


Target ≥ 50% LDL-C reduction
and LDL-C < 55 mg/dL
(or non-HDL-C < 85 mg/dL)
Maximally-tolerated statin
If LDL-C targets not reached
Consider adding ezetimibe and/or PCSK9 mAb¶
If LDL-C targets not reached
Consider referral to a lipid specialist and RD/RDN
If tolerability or adherence issues with PCSK9 mAbs§
Consider replacing PCSK9 mAb with inclisiran*
(if considering inclisiran, also consider referring to a lipid specialist)
If LDL-C targets not reached
Consider adding bempedoic acid*
If LDL-C targets not reached
Refer to a lipid specialist and RD/RDN
If inadequate response to maximally-tolerated statin with or without ezetimibe and PCSK9 inhibitors:
Consider (under care of lipid specialist):
• LDL apheresis (patients w/ HeFH or HoFH)
• Evinacumab* or lomitapide* (patients w/ HoFH)

¶ Simultaneous addition of two agents may be warranted in certain patients requiring greater LDL-C reduction than is likely achievable with one added therapy alone. If considering either ezetimibe or PCSK9 mAb, consider the following:

- **Ezetimibe** may be preferred as the initial nonstatin agent in those who require **< 25%** additional LDL-C reduction
- A **PCSK9 mAb** may be preferred as the initial nonstatin agent in those who require **> 25%** additional LDL-C reduction

*** No cardiovascular outcomes data** currently available for these agents *(for inclisiran, trial results are expected in 2026 and 2027)*

§ It should be noted that **inclisiran** is an alternative option for patients who are unable to fully benefit from PCSK9 mAbs due tolerability or adherence issues. Tolerability and adherence issues include **inability to self-administer.** PCSK9 mAbs are currently **preferred** over inclisiran based on available safety, efficacy, and cardiovascular outcomes data. If inclisiran is prescribed, it should **replace** the PCSK9 mAb, **not be used together**.

ASCVD: atherosclerotic cardiovascular disease
FH: familial hypercholesterolemia
HDL-C: high-density lipoprotein cholesterol
HeFH: heterozygous familial hypercholesterolemia
HoFH: homozygous familial hypercholesterolemia
LDL-C: low-density lipoprotein cholesterol
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Primary ASCVD Prevention: Baseline LDL-C ≥ 190 mg/dL

Target **≥ 50%** LDL-C reduction
and LDL-C **< 100 mg/dL**
(or non-HDL-C < 130 mg/dL)

Maximally-tolerated statin

If LDL-C targets not reached
Consider adding **ezetimibe** and/or **PCSK9 mAb**¶

If LDL-C targets not reached
Consider adding **second** nonstatin agent
(e.g., ezetimibe plus PCSK9 mAb)

If tolerability or adherence issues with PCSK9 mAbs§
Consider **replacing** PCSK9 mAb with **inclisiran***
(if considering inclisiran, also consider referring to a **lipid specialist**)

If LDL-C targets not reached
Consider adding **bempedoic acid***

If LDL-C targets not reached
Refer to a **lipid specialist** and **RD/RDN**

If LDL-C targets not reached
Consider referral to a **lipid specialist** and **RD/RDN**

If inadequate response to maximally-tolerated statin with or without ezetimibe and PCSK9 inhibitors:
Consider if HoFH (*under care of lipid specialist*):
- **LDL apheresis**
- **Evinacumab* or lomitapide***

¶ Simultaneous addition of two agents may be warranted in certain patients requiring greater LDL-C reduction than is likely achievable with one added therapy alone. If considering either ezetimibe or PCSK9 mAb, consider the following:
- **Ezetimibe** may be preferred as the initial nonstatin agent in those who require **< 25%** additional LDL-C reduction
- A **PCSK9 mAb** may be preferred as the initial nonstatin agent in those who require **> 25%** additional LDL-C reduction

*** No cardiovascular outcomes data** currently available for these agents *(for inclisiran, trial results are expected in 2026 and 2027)*

§ It should be noted that **inclisiran** is an alternative option for patients who are unable to fully benefit from PCSK9 mAbs due tolerability or adherence issues. Tolerability and adherence issues include **inability to self-administer.** PCSK9 mAbs are currently the **preferred** PCSK9 inhibitors over inclisiran based on available safety, efficacy, and cardiovascular outcomes data. If inclisiran is prescribed, it should **replace** the PCSK9 mAb, **not be used together**.

ASCVD: atherosclerotic cardiovascular disease
FH: familial hypercholesterolemia
HDL-C: high-density lipoprotein cholesterol
HoFH: homozygous familial hypercholesterolemia
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Primary ASCVD Prevention: Adults with Diabetes and Baseline LDL-C < 190 mg/dL

Age 20-39 Years

Initiation of statin may be reasonable in patients with *diabetes-specific risk enhancers**

Age 40-75 Years

10-year ASCVD risk ≥ 7.5%, diabetes-specific risk enhancers* or subclinical atherosclerosis?

- **No** → **Moderate-intensity statin**
  - Target **30-49%** LDL-C reduction and LDL-C **< 100 mg/dL** *(or non-HDL-C < 130 mg/dL)*
  - **If LDL-C targets not reached**
  - Increase to **high-intensity statin**
- **Yes** → **High-intensity statin**
  - Target **≥ 50%** LDL-C reduction and LDL-C **< 100 mg/dL** *(or non-HDL-C < 130 mg/dL)*
  - **If 10-yr ASCVD risk ≥ 20%:** Target **≥ 50%** LDL-C reduction and LDL-C **< 70 mg/dL** *(or non-HDL-C < 100 mg/dL)*
  - **If LDL-C targets not reached§**
  - Consider adding **ezetimibe**
  - **Optional alternative:** Consider **BAS** if fasting **TG < 300 mg/dL** and unable to tolerate or inadequate response to ezetimibe

Age > 75 Years

Reasonable to **continue** moderate or high-intensity statin if well-tolerated

Discuss the risks and benefits of pharmacotherapy (statins and nonstatins) **prior to initiation**

*ASCVD Risk Score ↗

*** Diabetes-Specific Risk Enhancers**

- Long duration of diabetes (≥ 10 years for type 2, ≥ 20 years for type 1)
- UACR ≥ 30
- eGFR< 60 mL/min
- Retinopathy
- Neuropathy
- ABI < 0.9

§ PCSK9 mAbs, inclisiran and bempedoic acid currently **do not** have an established place in therapy for primary prevention in patients with diabetes *(without ASCVD, baseline LDL-C ≥ 190 mg/dL, or significant subclinical atherosclerosis)*

ABI: ankle brachial index
ASCVD: atherosclerotic cardiovascular disease
BAS: bile acid sequestrant
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
PCSK9 mAb: proprotein convertase subtilisin/kexin type 9 monoclonal antibody
TG: triglyceride
UACR: urine albumin creatinine ratio

Reference: [1] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
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Primary ASCVD Prevention: Adults without Diabetes; Baseline LDL-C 70-189 mg/dL

Age 20-39 years:
Generally focus on implementing **healthy lifestyle changes** to reduce lifetime ASCVD risk

Age 40-75 Years
Assess 10-year ASCVD risk

Age > 75 years:
In patients with an LDL-C 70-189 mg/dL, initiation of a **moderate-intensity statin** may be reasonable upon **discussion**

< 5% *Low-Risk*	**5% to < 7.5%** *Borderline-Risk*	**≥ 7.5% to < 20%** *Intermediate-Risk*	**≥ 20%** *High-Risk*
Promote healthy lifestyle to reduce ASCVD risk	Consider risk-enhancing factors* and **discuss moderate-intensity statin therapy**	Consider **moderate-intensity statin therapy**	**High-intensity statin** Target **≥ 50%** LDL-C reduction and LDL-C **< 70 mg/dL** *(or non-HDL-C < 100 mg/dL)*
	Target **30-49%** LDL-C reduction and LDL-C **< 100 mg/dL** *(or non-HDL-C < 130 mg/dL)*		**If LDL-C targets not reached** Consider adding **ezetimibe****
	If LDL-C targets not reached Increase to **high-intensity statin**		

*ASCVD Risk Score ↗

If there is **clinical uncertainty** regarding the need for statin therapy in patients with **borderline-** or **intermediate-risk**, their **CAC score** may be used to help reach a decision

CAC = 0 AU	Consider **deferring statin** & reassess in 3-5 years *(if no high-risk conditions present)*		
CAC 1-99 AU and < 75th percentile *(for corresponding age/sex/race)*	Consider **moderate-intensity statin**	Target **30-49%** LDL-C ↓ LDL-C **< 100 mg/dL**	If LDL-C targets not reached, consider **high-intensity statin**
CAC ≥ 100 AU or ≥ 75th percentile *(for corresponding age/sex/race)*	Consider **moderate- or high-intensity statin**	Target LDL-C ↓ based on statin intensity; LDL-C **< 70 mg/dL**	If LDL-C targets not reached, **consider ezetimibe**
CAC ≥ 1000 AU	Consider **high-intensity statin**	Target **≥ 50%** LDL-C ↓ LDL-C **< 70 mg/dL**	If LDL-C targets not reached, **consider ezetimibe, then PCSK9 mAb**

*** Risk-enhancing factors**

Medical History/Demographics
- Family history of premature ASCVD (males < 55 years; females < 65 years)
- Primary hypercholesterolemia (LDL-C 160-189 mg/dL)
- Chronic kidney disease (with or without albuminuria)
- Metabolic syndrome
- History of premature menopause (before age 40) or preeclampsia
- Chronic inflammatory disorders (e.g., psoriasis, RA, HIV/AIDS)
- High-risk race/ethnicities (e.g., South Asian ancestry)

Biomarkers
- Persistently elevated, primary hypertriglyceridemia (≥ 175 mg/dL)
- CRP ≥ 2.0 mg/dL
- Lp(a) level ≥ 50 mg/dL (or >125 nmol/L)
- apoB ≥ 130 mg/dL
- Ankle-brachial index (ABI) <0.9

****** The use of PCSK9 mAbs is **not routinely recommended** for primary prevention in these patients due to limited data

AIDS: acquired immunodeficiency syndrome
ASCVD: atherosclerotic cardiovascular disease
apoB: apolipoprotein B
AU: Agatston unit
CAC: coronary artery calcium
CRP: C-reactive protein
HDL-C: high-density lipoprotein cholesterol
HIV: human immunodeficiency virus
LDL-C: low-density lipoprotein cholesterol
Lp(a): lipoprotein (a)
PCSK9 mAb: proprotein convertase subtilisin/kexin type 9 monoclonal antibody
RA: rheumatoid arthritis

Reference: [1] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
[2] Writing Committee, Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006

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